underlining. A clean version of the pending claims, as amended, is attached hereto as Exhibit B.

Please amend the claims as follows:

Please amend claims 1, 18, 26, 29, 31, 38-39, 50, 64, 72, 96, 106 and 123 to read as follows:

1. (Six Times Amended) A method of determining a consensus profile for a first plurality of drug perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of cellular constituents in a plurality of response profiles, whether said set of cellular constituents is upregulated or downregulated by each of said first plurality of drug perturbations, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different drug perturbation among said first plurality of drug perturbations to said type of cell or organism, wherein each set of cellular constituents in said plurality of sets of cellular constituents consists of cellular constituents that co-vary under a second plurality of perturbations or that are co-regulated, wherein said plurality of response profiles comprises at least five response profiles, and wherein said consensus profile for said first plurality of drug perturbations consists of measurements of said set or sets of cellular constituents that are determined in said determining step to be upregulated or downregulated by each of said first plurality of drug perturbations.

18. (Three Times Amended) The method of claim 17, wherein said cluster analysis is carried out by a hierarchical clustering method, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of co-varying cellular constituents an actual fractional improvement in the cluster analysis of the cellular constituents based on the unpermuted responses of said cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted responses of cellular constituents by means of Monte Carlo randomization of perturbation index for the response of each cellular constituent across all perturbations;

(c) performing said cluster analysis on the permuted responses of cellular constituents;

(d) determining for each cluster which is generated in step (c) and defines a set of co-varying cellular constituents the fractional improvement in the cluster analysis of cellular constituents based on the permuted responses of cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the cellular constituents is obtained for each said cluster which is generated by said cluster analysis and defines a set of co-varying cellular constituents;

wherein the statistical significance of each of said sets of co-varying cellular constituents is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

26. (Three Times Amended) The method of claim 25, wherein said cluster analysis is carried out by a hierarchical clustering method, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of response profiles an actual fractional improvement in the cluster analysis of the unpermuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted response profiles by means of Monte Carlo randomization of cellular constituent index for each response profile across the measured cellular constituents;

(c) performing said cluster analysis on the permuted response profiles;

(d) determining for each cluster which is generated in step (c) and defines a set of response profiles the fractional improvement in the cluster analysis of the permuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the response profiles is obtained for each said cluster which is generated by said cluster analysis and defines a set of response profiles;

wherein the statistical significance of each of said sets of response profiles is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

29. (Four Times Amended) A method of determining a consensus profile for a first plurality of perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of cellular constituents in a plurality of projected profiles, whether said set of cellular constituents is upregulated or downregulated by each of said first plurality of perturbations, each projected profile in said plurality of projected profiles

(i) resulting from a different perturbation among said first plurality of perturbations to said type of cell or organism, and

(ii) comprising measurements of a plurality of cellular constituents in said type of cell or organism that have been projected onto basis cellular constituent sets, said basis cellular constituent sets being defined by co-variation of measurements of cellular constituents under a second plurality of different perturbations, wherein said consensus profile for said first plurality of perturbations consists of projected measurements of said set or sets of cellular

constituents that are determined in said determining step to be upregulated or downregulated by each of said first plurality of perturbations.

31. (Three Times Amended) The method of claim 29, wherein the consensus profile is the intersection of the sets of cellular constituents activated or de-activated by each of said first plurality of perturbations.

38. (Five Times Amended) A method of determining a consensus profile for a first plurality of perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of genes in a plurality of response profiles, whether said set of genes is upregulated or downregulated by each of said first plurality of perturbations, each response profile in said plurality of response profiles (i) comprising measurements of transcript levels for a plurality of genes, and (ii) resulting from a different perturbation among said first plurality of perturbations to said type of cell or organism, wherein each set of genes in said plurality of sets of genes consists of genes having transcripts that co-vary under a second plurality of perturbations or that are co-regulated, and wherein said consensus profile for said first plurality of perturbations consists of measurements of transcript levels for said set or sets of genes that are determined in said determining step to be upregulated or downregulated by each of said first plurality of perturbations.

39. (Three Times Amended) A method for comparing a biological response profile to a consensus profile, said consensus profile consisting of projected measurements of one or more sets of cellular constituents, said one or more sets having been identified among a plurality of sets of cellular constituents in a plurality of projected response profiles, each of said one or more sets of cellular constituents being upregulated or downregulated by each of said first plurality of perturbations, each projected response profile in said plurality of projected response profiles

(i) resulting from a different perturbation to said type of cell or organism, and

(ii) comprising measurements of a plurality of cellular constituents in said type of cell or organism that have been projected onto basis cellular constituent sets, said basis cellular

constituent sets being defined by co-variation of measurements of cellular constituents under a second plurality of different perturbations, said method comprising:

(a) converting the biological response profile into a projected response profile by projecting measurements of cellular constituents in said biological response profile onto said basis cellular constituent sets; and

(b) determining the value of a similarity metric between the projected response profile and the consensus profile.

50. (Three Times Amended) The method of claim 49, wherein said cluster analysis is carried out by a hierarchical clustering method, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of response profiles an actual fractional improvement in the cluster analysis of the unpermuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted response profiles by means of Monte Carlo randomization of gene index for each response profile across the measured genes;

(c) performing said cluster analysis on the permuted response profiles;

(d) determining for each cluster which is generated in step (c) and defines a set of response profiles the fractional improvement in the cluster analysis of the permuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the response profiles is obtained for each cluster which is generated by said cluster analysis and defines a set of response profiles;

wherein the statistical significance of each of said sets of response profiles is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

64. (Three Times Amended) The method of claim 63, wherein said cluster analysis is carried out by a hierarchical clustering method, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of cellular constituents an actual fractional improvement in the cluster analysis of cellular constituents based on the unpermuted responses of said cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted responses of cellular constituents by means of Monte Carlo randomization of the perturbation index for each cellular constituent across all perturbations;

(c) performing said cluster analysis on the permuted responses of cellular constituents;

(d) determining for each cluster which is generated in step (c) and defines a set of cellular constituents the fractional improvement in the cluster analysis of cellular constituents based on the permuted responses of cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the cellular constituents is obtained for each cluster which is generated by said cluster analysis and defines a set of cellular constituents;

wherein the statistical significance of each of said sets of cellular constituents is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

72. (Four Times Amended) A method for analyzing response data from a biological sample comprising

(a) grouping genes from the biological sample into sets of genes that co-vary in a plurality of response profiles, each response profile in said plurality of response profiles (i) comprising measurements of transcript levels of a plurality of genes, and (ii) resulting from a different perturbation to said biological sample; and

(b) grouping the plurality of response profiles into sets of response profiles that have similarly affected genes,

wherein said plurality of response profiles comprises at least five response profiles.

96. (Twice Amended) The method of claim 95, wherein said cluster analysis is carried out by a hierarchical clustering method, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of co-varying cellular constituents an actual fractional improvement in the cluster analysis of the cellular constituents based on the unpermuted responses of said cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted responses of cellular constituents by means of Monte Carlo randomization of the perturbation index for response of each cellular constituent across the set of perturbations;

(c) performing said cluster analysis on the permuted responses of cellular constituents;

(d) determining for each cluster which is generated in step (c) and defines a set of co-varying cellular constituents the fractional improvement in the cluster

analysis of cellular constituents based on the permuted response responses of cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the cellular constituents is obtained for each cluster which is generated by said cluster analysis and defines a set of co-varying cellular constituents,

wherein the statistical significance of each of said sets of co-varying cellular constituents is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

106. (Twice Amended) The method of claim 105, wherein said cluster analysis is carried out by a hierarchical clustering method, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of response profiles an actual fractional improvement in the cluster analysis of the unpermuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted response profiles by means of Monte Carlo randomization of cellular constituent index for each response profile across the measured cellular constituents;

(c) performing said cluster analysis on the permuted response profiles;

(d) determining for each cluster which is generated in step (c) and defines a set of response profiles the fractional improvement in the cluster analysis of the permuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as

compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the response profiles is obtained for each cluster which is generated by said cluster analysis and defines a set of response profiles;

wherein the statistical significance of each of said sets of response profiles is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

123. (Twice Amended) The method of claim 122, wherein said cluster analysis is carried out by a hierarchical clustering method, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of co-varying genes an actual fractional improvement in the cluster analysis of the genes based on the unpermuted responses of said genes, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted responses of genes by means of Monte Carlo randomization of perturbation index for the response of each gene across all perturbations;

(c) performing cluster analysis on the permuted responses of genes;

(d) determining for each cluster which is generated in step (c) and defines a set of co-varying genes the fractional improvement in the cluster analysis of genes based on the permuted responses of genes, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the genes is obtained for each cluster